Improving microenvironments to promote hematopoietic stem cell development from human embryonic stem cells

Grant Award Details

Improving microenvironments to promote hematopoietic stem cell development from human embryonic stem cells

Grant Type: SEED Grant

Grant Number: RS1-00420

Project Objective: We will exploit our understanding of embryonic hematopoiesis to develop culture conditions and in vivo models that mimic the natural microenvironments where human HSCs develop

Investigator:

Name:	Hanna Mikkola
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Blood Disorders

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $550,241

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: NCE

View Report

Grant Application Details

Application Title: Improving microenvironments to promote hematopoietic stem cell development from human embryonic stem cells

Public Abstract:

Hematopoietic stem cells (HSC) have been used successfully to cure various life-threatening blood diseases. Yet, matching HSCs are not available for every patient. Human embryonic stem cells (hESC) may provide an unlimited source of HSCs for therapeutic use. However, hESC derived hematopoietic cells do not develop properly in those culture conditions that are currently used, and thereby their function is impaired. Hematopoietic cells that are derived from human ES cells lack the ability to self-renew, which is a prerequisite for the ability to generate blood cells for the individual's lifetime. HSCs can only develop and function normally if they receive correct signal from their microenvironment, the stem cell niche. The goal of our proposal is take advantage of our knowledge of development of hematopoietic stem cells during embryogenesis, and mimic the environments where HSCs normally develop to provide the cues for proper HSC development in culture. We will attempt to mimic physiological HSC niches by deriving stroma lines from human placentas, which we have shown to be an important site for HSC development. We will further modify these lines by adding regulatory molecules that are known to aid HSC self-renewal, or inhibit molecules that might promote premature differentiation. Alternatively, we will use placental villi as a niche where ES cell derived hematopoietic cells could develop during culture. Subsequently, hESC derived cells are tested in animal models where human hematopoietic tissues have been implanted to provide an optimal environment for human HSCs to function. These studies are expected to shed light on the mechanisms that enable human HSCs to establish and maintain self-renewal ability and multipotency, and improve the differentiation of hESCs towards functional HSCs, which could be used to treat leukemias, other cancers, and inherited disease of the blood and immune system. To ensure hESC lines derived in different conditions respond in a similar way to these developmental cues, non-federally approved lines have to be used in this study, and thus governmental funding is not attainable for this project {REDACTED}.

Statement of Benefit to California:

We aim to develop hematopoietic stem cells (HSC) from human ES cells (hESC) for ultimate theraoutic use for blood diseases. Only up to 50% of the patients that could be cured by HSC transplantation are able to receive this treatment, as matching donors are not available for every patient. If functional HSCs could be generated from hESCs, patients in California that suffer from leukemias or other acquired or inherited diseases of the blood and immune system could be treated.

We aim to develop novel approaches to differentiate HSCs from hESCs by mimicking the physiological niches where human HSCs normally develop. Through these studies, we aim to understand what the critical properties in HSC microenvironment are that signal for HSCs to preserve their functionality. Identification of the regulatory cues that alter HSC fates between self-renewal and differentiation might also lead to innovative discoveries that could be developed into biotechnological or pharmaceutical products in California, thereby improving the industry and economy in California.
